REMARKS

Claim 18 has been amended simply for clarification. Claim 1 has been amended by inserting the required steps set forth in claim 19. Clearly this does not raise new issues as it amounts simply to the cancellation of claim 1 in favor of claim 19, and disposes of the rejection under 35 U.S.C. § 102. Accordingly, entry of the amendment, though made after final rejection, is respectfully requested.

The Invention

The invention resides in the discovery that enhancing the temperature of an imaging agent that comprises liquid nanoparticles, without causing the liquid to vaporize into gas, can enhance the reflectivity of a target and thus enhance the quality of the image formed from the target. As will further be explained below, nothing in the cited art suggests doing this or suggests this effect.

Enclosed herewith is the Declaration of Dr. Gregory M. Lanza which explains that the hyperthermia created in the surrounding tissue by the method of Unger '319 is unrelated to the method of the invention which raises the temperature not of the surrounding tissue but of the nanoparticles themselves so as to obtain a better reflectivity or image from a targeted tissue, not to use heat to destroy unwanted tissue.

The Rejection Under 35 U.S.C. § 112, Paragraph 2

All claims were rejected as assertedly incomplete for omitting the "essential step" of administering the liquid nanoparticles to the target site. Respectfully, applicants call the attention of the Office to the last phrase in each of claims 1 and 18 which reads "said nanoparticles having been administered to said target in a non-gaseous emulsion." As far as applicants are aware, there is no necessity for including this administration as an active step.

Applicants believe they are entitled to claims which would be infringed by the steps of changing the temperature of the nanoparticles while at the target and obtaining an ultrasound image (claim 18) or measuring the reflectivity prior to raising the temperature of bound nanoparticles changing the temperature, again measuring the reflectivity and determining the change in reflectivity (claim 1). The step of administering the nanoparticles in a non-gaseous emulsion may have been done by another individual. This basis for rejection, respectfully, may properly be withdrawn.

The Rejection for Anticipation

Claims 1, 8, 13 and 68-71 were rejected as assertedly anticipated under 35 U.S.C. § 102(b) by Milbrath, U.S. patent 5,401,634. Neither claim 18 nor claim 19 were included in this rejection and properly so since claim 18 requires obtaining an image and claim 19 requires measuring reflectivity at various points. Neither of these is done in Milbrath. As the limitations of claim 19 have been added to claim 1, the rejection on this basis is overcome with respect to that claim and any claims dependent thereon including claims 8, 13 and 68-71. Accordingly, this basis for rejection may properly be withdrawn.

The Rejection Under 35 U.S.C. § 103

All claims were rejected under this section over the combination of Unger, U.S. patent 5,149,319 and Trevino, U.S. patent 5,733,526, taken in view of Allen, *et al.,* U.S. patent 5,527,528 and Unger, *et al.,* U.S. patent 6,123,923.

The Office first states that applicants have disregarded the general knowledge that fluorochemicals when exposed to ultrasound energy are known to cause hyperthermia. This is not the case; this knowledge is simply not germane to the invention. The invention does not lie in any asserted discovery that ultrasound may be used to raise the temperature at a local site; the

invention as claimed is directed to enhancing the reflectivity of nanoparticles targeted to a site. Indeed, the temperature that is desired to be changed, as set forth in claims 1 and 18, is the temperature of the "liquid nanoparticles bound to said target" not the target itself. Respectfully, applicants believe the Office will look in vain for any documents that alone or together suggest that an image could be enhanced, or reflectivity of targeting nanoparticles increased, by raising the temperature of the nanoparticles themselves.

The Office directs attention to the disclosure of Unger '319 as disclosing the ability of certain materials, including perfluorocarbons, to potentiate the hyperthermia effect of ultrasound. Again, the ability of ultrasound itself to effect a temperature increase in perfluorocarbons is known and acknowledged. Contrary to the assertion of the Office, however, Unger does not teach the active step of monitoring the progress of the treatment with an ultrasound probe in examples 5-10, or in any other examples or any other place that applicants are able to find. (See also the Declaration of Dr. Lanza, paragraphs 3, 9 and 10.) There is no mention in examples 5-10 of any ultrasound probe; the only mention of ultrasound is to expose the "potentiator" to ultrasound energy in order to induce a temperature rise. The only mention of monitoring the tumor or surrounding tissue is in column 11, at line 5; it appears clear from the context that what is meant is monitoring the temperature of the tumor and surrounding tissue. This is a line of distinction; as will be evident from the enclosed declaration of Dr. Gregory Lanza, the invention methodology requires enhancing the temperature of the nanoparticles themselves, not the surrounding tissue as described by Unger, as well as the further step of measuring reflectivity.

In addition to the fact that Unger simply does not recite any of the required steps of the claim involving measuring reflectivity or obtaining an image of a target, the type of ultrasound

that would be useful in what Unger does describe is of a different nature that the ultrasound signal that would be used to obtain an image or measure reflectivity. Dr. Lanza's declaration describes this difference in paragraph 4. In order to generate heat with ultrasound, low frequency, steady beams of ultrasound would be employed; whereas in order to obtain an image or to measure reflectivity, short, higher frequency pulses would be used. As explained in Dr. Lanza's declaration in paragraphs 6-8, the hypothetical examples in Unger actually employ what would be clear to one skilled in the art as an ultrasound frequency which, while less than that useful for obtaining images, is higher than would be effective in elevating the temperature of the surrounding tissue.

It is thus not the case that, as is asserted by the Office, Unger's only shortcoming is lack of an explicit teaching that his compositions are bound to the target site. On the contrary, Unger's deficiency is in failing to teach, even inherently, that the ultrasound image obtained by increasing the temperature of the nanoparticles (as opposed to the target tissue) would enhance the image or reflectivity of the target. (Of course, the Office is correct that Unger does indeed fail to teach targeting of the nanoparticles, an essential element of the claims.) None of Trevino, Allen or Unger '923 remedy the fundamental defect of the primary reference, Unger '319 – that this document fails to teach actually imaging or measuring reflectivity of the nanoparticles at elevated temperatures.

The Office correctly characterizes Trevino as simply disclosing microemulsions for the administration of therapeutic agents (different from those of the present invention in requiring a hydrocarbon oil, which the emulsions of the present invention do not exclude but do not require). The emulsions of Trevino are said to be used simply for "controlled administration of bioactive agents" (column 7, line 66). Applicants do not find any mention in Trevino of the use of the

disclosed emulsions as diagnostics; rather they are designed for delivery of a bioactive agent. Therefore, Trevino seems relevant at best only to claims 8 and 26. Trevino contains no discussion of ultrasound imaging or reflectivity at all.

Allen is said to be cited only to show that targeting lipid vesicles is known. Allen, however, again concerns only the use of liposomes (not fluorocarbon nanoparticles) for drug delivery, not imaging. Allen describes an entirely different type of composition for an entirely different purpose.

Unger '923 is apparently cited to show targeting ligands and ultrasound imaging; nothing in Unger '923 suggests raising the temperature of any imaging agent in order to enhance reflectivity. Indeed, the section noted in column 121, where imaging by ultrasound is conducted, requires a gas or a gas precursor as the image enhancer, contrary to the requirement in the present invention for liquid nanoparticles.*

In sum, the combination of Unger '319 with Trevino, Allen and Unger '923 does not suggest the invention even if the combination is made. Applicants respectfully submit that the Office has pointed to nothing in any document alone or in combination that suggests elevating the temperature of targeted nanoparticles in order to enhance the reflectivity of the target and actually measuring the reflectivity or obtaining an image – *i.e.*, a reflection from the target. It is this that constitutes the invention and nowhere in any of the documents alone or in combination is this suggested.

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* It should be noted that targeting is an essential feature of the invention as claimed. Since it is desired to enhance the reflectivity of only the target, so as better to contrast with its surroundings, the nanoparticles must be confined to the target. Targeting is essential in the present invention because the object is to provide enhanced reflection from the target itself, and not the surroundings of the target. Since Unger uses only the ultrasound itself to confine the temperature elevation to a particular location, there is no way that the reflectivity at the target could be enhanced as compared to the surrounding tissue using the Unger approach. (See Dr. Lanza's declaration, paragraph 10.)

Further, there is no motivation shown to combine these documents. (Even the invention does not suggest their combination, since the invention is about something else entirely.) The Office asserts that it would be within skill of the art at the time of the invention to optimize the particle sizes of Unger's '319 composition as taught by Trevino; however, there is no suggestion in Unger that the particle sizes of Unger's composition need any optimizing and, in any event, Trevino is directed to delivering bioactive agents, and not to supplying hyperthermia to surrounding tissue. The Office further suggests that it would be obvious to link a targeting ligand to the particles of Unger by well known methods such as taught by Allen and Unger '923, but there is no suggestion in Unger that the particles need to be targeted and Allen is directed to a different purpose from Unger '319 – *i.e.*, administering antitumor compounds and Unger '923 is directed to a different purpose as well – obtaining a combined optical and acoustic image. The Office further suggests that it would be obvious to use ultrasound as taught by Unger (presumably '923) to detect the location of the administered nanoparticles at the site of interest (it should be noted that Unger '319 makes no such suggestion, contrary to the position taken by the Office). The ultrasound imaging suggested by Unger '923 is, contrary to the case for the present invention, limited to nanoparticles which are gases or gaseous precursors. The claims require liquid nanoparticles. In any event, the thrust of the disclosure of Unger '923 is the delivery of a photoactive agent in addition to an acoustic agent so that both an optical and acoustic image can be taken. There is nothing in Unger '923 that suggests its combination with anything else, much less the other documents cited by the Office.

In view of the foregoing discussion, and in view of the Declaration of Dr. Gregory Lanza, it is respectfully submitted that this basis for rejection may be withdrawn.

CONCLUSION

The presence of the step of administering the emulsions of the invention to the target in claims 1 and 18 has been pointed out, thus overcoming the rejection under 35 U.S.C. § 112, second paragraph. The amended claims were not subject to rejection for anticipation over Milbrath. The rejection for obviousness based on a combination of documents overlooks the essential elements of the invention which are suggested nowhere in these documents either alone or in combination. Further, no motivation to combine these documents has been shown. Accordingly, it is believed that claims 1, 3, 7-8, 13, 17-18, 21, 25-26, 31, 35 and 68-77 are in position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000500.

Respectfully submitted,

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